

REMARKS/ARGUMENTS

Claims 63, 69 and 70 are currently pending in the instant application.

I. Claim Rejections Under 35 U.S.C. §§101 and 112, First Paragraph (Enablement)

Claims 63, 69 and 70 remain rejected under 35 U.S.C. §101 and 112, first paragraph, allegedly "because the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility", and therefore one skilled in the art clearly would not know how to use the claimed invention. (Page 3 of the instant Final Office Action).

Applicants strongly disagree and, therefore, respectfully traverse the rejection.

Applicants submit that the data presented in Example 114 of the specification, and the cumulative evidence of record, indeed support a "specific, substantial and credible" asserted utility for the presently claimed invention. Applicants rely upon the gene amplification data of the PRO213-1 gene for patentable utility of the claimed PRO213-1 polypeptides. This data is clearly disclosed in the instant specification in Example 114, which discloses that the gene encoding PRO213-1 showed significant amplification in primary lung and colon tumors. As disclosed in previous response on record, Applicants submit that one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO213-1 gene, that the PRO213-1 polypeptide is concomitantly over expressed and has utility in the diagnosis of lung and colon cancers or for individuals at risk for developing lung or colon cancers.

Applicants submit that a ΔCt value of at least 1.0 was observed for PRO213-1 in at least nineteen of the lung tumors or lung cancer cell lines and sixteen of the colon tumors or colon cancer cell lines. Table 9 teaches that the nucleic acids encoding PRO213-1 showed approximately 1.03-5.55 ΔCt units which corresponds to 2.04 fold to 46.9-fold amplification in samples from lung tumors or lung cancer cell lines, and showed approximately 1.18-3.79 ΔCt units which corresponds to 2.27 fold to 13.8-fold amplification in the samples from primary colon tumors or colon cancer cell lines. Accordingly, the present specification clearly discloses overwhelming evidence that the gene encoding the PR0213-1 polypeptide is significantly amplified in lung and colon tumors.

As further support for their utility claim, Applicants have submitted a Declaration by Dr. Audrey Goddard (made of record in the Response submitted October 4, 2004), which explains

that a gene identified as being amplified at least 2-fold by the disclosed gene amplification assay in a tumor sample relative to a normal sample is useful as a marker for the diagnosis of cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. Therefore, such a gene is useful as a marker for the diagnosis of lung cancer, and for monitoring cancer development and/or for measuring the efficacy of cancer therapy. According to the Goddard Declaration, the 2.04 fold to 46.9-fold amplification of the PRO213-1 gene in lung and colon tumors would be considered significant and credible by one skilled in the art, based upon the facts disclosed therein. The Examiner has not provided any evidence to show that the disclosed DNA amplification is not significant.

The Examiner asserts that the Goddard declaration is not persuasive and alleges that the significance of the amplification can be questioned based on "the absence of factual support for the expert's opinion." Further, the Examiner asserts that "while the Goddard declaration speaks to the utility and enablement of genes, it does not speak to whether or not the encoded proteins are also found at increased levels in cancerous tissues (Pages 9-10 of the instant Final Office Action).

Applicants submit that the Goddard Declaration was presented to show what delta Ct values were considered significant in the TaqMan[®] assay. The deltaCt values for PR0213-1 of at least 1.03-5.55 ΔCt units, which correspond to 2.04-fold to 46.9-fold amplification in primary lung and colon tumors, were considered significant according to the Goddard declaration. The formula for showing how the data was analyzed has been clearly disclosed in the specification in Example 114. As explained in Example 114, "the results of TaqMK™ PCR are reported in ~Ct units. One unit corresponds to one PCR cycle or approximately a 2-fold amplification, relative to control, two units correspond to 4-fold, 3 units to 8-fold amplification and so on" (emphasis added). Table 9 indicates that PR0213-1 showed approximately 1.03-5.55 ΔCt units which corresponds to $2^{1.03} - 2^{5.55}$ -fold amplification or 2.04-fold to 46.9-fold amplification in lung and colon tumors, which is significant and thus the PR0213-1 gene has utility as a diagnostic marker of human lung and colon cancers.

Applicants submit that Dr. Goddard's declaration is based on Dr. Goddard's personal experience handling large databases of human tumor samples in the SPDI project and on personal experience with the Taqman[®] assay, as is clearly disclosed in the Declaration. The Examiner has to view the statements in the declaration with the total evidence presented in this

case. The case law has clearly established that in considering affidavit evidence, the Examiner must consider all of the evidence of record anew (*In re Rinehart*, 531 F.2d 1084, 189 USPQ 143 (C.c.P.A. 1976); *In re Piasecki*, 745F.2d. 1015,226 USPQ 881 (Fed. Cir. 1985)). "After evidence or argument is submitted by the applicant in response, patentability is determined on the totality of the record, by a preponderance of the evidence with due consideration to persuasiveness of argument." (*In re Alton*, 37 USPQ2d 1578, 1584 (Fed. Cir 1996) (quoting *In re Oetiker*, 977 F.2d 1443, 1445,24 USPQ2d 1443, 1444 (Fed. Cir. 1992)). Furthermore, the Federal Court of Appeals held in *In re Alton*, "We are aware of no reason why opinion evidence relating to a fact issue should not be considered by an Examiner (*In re Alton, supra.*). Applicants also respectfully draw the Examiner's attention to the Utility Examination Guidelines (Part II B, 66 Fed. Reg. 1098 (2001)) which state, "Office personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being questioned; it is improper to disregard the opinion solely because of a disagreement over the significance or meaning of the facts offered." Applicants submit that the Patent Office has failed to provide substantial evidence for disregarding the Goddard Declaration.

The Examiner addresses the pooled blood controls used in the gene amplification assay and asserts that the controls were not matched, non-tumor lung samples, but rather pooled DNA samples from blood of healthy subjects. (Pages 9 and 10 of the instant Final Office Action)

Applicants respectfully submit that the Examiner's position is incorrect because the instant application relies on **genomic DNA** amplification for utility and not cDNA expression. Different types of cells from the same organism should have the same set of genomic DNA. Thus, it does not matter what kind of cells you use for the control as long as the control cells have the entire genome. Accordingly, a "tissue-matched" control is not necessary in the gene amplification assay.

Applicants further point out that Pennica *et al.* teaches the exact same "pooled normal blood controls" as that used in the instant gene amplification assay (for instance, see page 14718, column 1 and Figure 5 of Pennica *et al.*). Further, the references Bieche *et al.* and Pitti *et al.*, submitted as Exhibits F and G with the Goddard Declaration, also used "pooled normal blood controls" as control. For instance, in Pitti *et al.* the authors used the same quantitative TaqMan PCR assay and pooled normal blood controls described in the instant specification, to study gene

amplification in lung and colon cancer of DcR3, a decoy receptor for Fas ligand. Pitti *et al.* analyzed DNA copy number "in genomic DNA from 35 primary lung and colon tumors, relative to pooled genomic DNA from peripheral blood leukocytes (PBL) of 10 healthy donors." (Page 701, col. 1). The authors also analyzed mRNA expression of DcR3 in primary tumor tissue sections and found tumor-specific expression, confirming the finding of frequent amplification in tumors, and confirming that the pooled blood sample was a valid negative control for the gene amplification experiments. In Bieche *et al.*, the authors used the quantitative TaqMan PCR assay to study gene amplification of myc, cend1 and erbB2 in breast tumors. As their negative control, Bieche *et al.* used normal leukocyte DNA derived from a small subset of the breast cancer patients (page 663). The authors note that "[t]he results of this study are consistent with those reported in the literature" (page 664, col. 2). Thus, contrary to the Examiner's allegations, Pennica *et al.*, Pitti *et al.* and Bieche *et al.* in fact, confirm the validity of use of the "pooled blood control" as a negative controls, and indicate that this control was widely utilized in the art at the time of filing of the instant application.

*The Examiner further asserts that the data presented in the specification were not corrected for aneuploidy and cites references by Hittelman *et al.* and Sen *et al.* in support of the assertion that "[a] slight amplification of a gene does not necessarily correlate with overexpression in a cancer tissue, but can merely be an indication that the cancer tissue is aneuploid."* (Pages 4-6 of the instant Final Office Action).

Applicants submit that it is known in the art that detection of gene amplification can be used for cancer diagnosis regardless of whether the increase in gene copy number results from intrachromosomal changes or from chromosomal aneuploidy. As explained by Dr. Ashkenazi in his Declaration (submitted with Applicants' Response filed October 4, 2004),

An increase in gene copy number can result not only from intrachromosomal changes but also from chromosomal aneuploidy. It is important to understand that detection of gene amplification can be used for cancer diagnosis even if the determination includes measurement of chromosomal aneuploidy. Indeed, as long as a significant difference relative to normal tissue is detected, it is irrelevant if the signal originates from an increase in the number of gene copies per chromosome and/or an abnormal number of chromosomes.

Hence, Applicants submit that gene amplification of a gene, whether by aneuploidy or any other mechanism, is useful as a diagnostic marker.

Regarding Sen and Hittelman, Applicants agree that while aneuploidy can be a feature of damaged tissue as well, besides cancerous or pre-cancerous tissue, and may not invariably lead to cancer, Sen *et al.* in fact support the Applicants' position that PRO213-1 is still useful in diagnosing pre-cancerous lesions or cancer itself. For instance, the art in lung cancer at the time of filing of the instant application clearly described that "epithelial tumors develop through a multistep process driven by genetic instability" in damaged lung lesions which may eventually lead to lung cancer. Many articles published around the effective filing date of this application studied such damaged or premalignant lesions and suggested that identification of such pre-cancerous lesions were very important in preventive diagnosis and treatment of lung cancer. Based on the well-known art, Applicants submit that there is utility in identifying genetic biomarkers in epithelial tissues at cancer risk.

The Examiner asserts that "[i]n order for PRO213-1 polypeptides to be overexpressed in tumors, amplified genomic DNA would have to correlate with increased mRNA levels and increased polypeptide levels. No data regarding PRO213-1 mRNA or PRO213-1 polypeptide levels in lung tumors have been brought forth on the record." (Page 5 of the instant Final Office Action).

The Examiner's reference to the lack of necessary correlation or accurate prediction in some of the rejections clearly shows that the Examiner applies an improper legal standard when making this rejection. The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the totality of the evidence under consideration. Thus, to overcome the presumption of truth that an assertion of utility by the Applicant enjoys, the Examiner must establish that it is more likely than not that one of ordinary skill in the art would doubt the truth of the statement of utility. Only after the Examiner has made a proper *prima facie* showing of lack of utility, does the burden of rebuttal shift to the Applicant. As discussed below, the references cited by the Examiner do not suffice to make a *prima facie* case that more likely than not no generalized correlation exists between gene (DNA) amplification and increased polypeptide levels.

In contrast, Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (made of record in Applicants' Response filed October 4, 2004) collectively teach that in general, gene amplification increases mRNA expression. Second, the Declarations of Dr. Paul Polakis (made of record in Applicants' Response of October 4, 2004 and Preliminary Amendment of July 7, 2006, principal investigator of the Tumor Antigen Project of Genentech, Inc., the assignee of the present application, shows that, in general, there is a correlation between mRNA levels and polypeptide levels. Applicants further note that, as supported by the Declaration of Dr. Randy Scott (made of record in Applicants' Supplemental Preliminary Amendment filed September 6, 2006), the sale of gene expression chips to measure mRNA levels is a highly successful business, with a company such as Affymetrix recording 168.3 million dollars in sales of their GeneChip arrays in 2004. Clearly, the research community believes that the information obtained from these chips is useful (*i.e.*, that it is more likely than not informative of the protein level).

Accordingly, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO213-1 gene, that the PRO213-1 polypeptide is concomitantly overexpressed. Thus, the claimed PRO213-1 polypeptides have utility in the diagnosis of cancer.

The Examiner asserts that “[s]ignificant further research would have been required of the skilled artisan to reasonably confirm that PRO213-1 is overexpressed in any cancer to the extent that it could be used as a cancer diagnostic agent; thus the asserted utility is not substantial.” (Page 8 of the instant Final Office Action).

As discussed in previous responses of record, M.P.E.P. §2107.01 cautions Office personnel not to interpret the phrase “immediate benefit to the public” or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be “currently available” to the public in order to satisfy the utility requirement. “Rather, any reasonable use that an Applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient, at least with regard to defining a ‘substantial’ utility.”¹ Indeed, the Guidelines for Examination of Applications for Compliance

¹ M.P.E.P. §2107.01.

With the Utility Requirement,² gives the following instruction to patent examiners: "If the Applicant has asserted that the claimed invention is useful for any particular practical purpose . . . and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Applicants' position is based on the overwhelming evidence from gene amplification data disclosed in the specification which clearly indicate that the gene encoding PRO213-1 is significantly amplified in certain lung and colon tumors. Based on the working hypothesis among those skilled in the art that if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level, one skilled in the art would simply accept that since the PRO213-1 gene is amplified, the PRO213-1 polypeptide would be more likely than not over-expressed. Thus, data relating to PRO213-1 polypeptide expression may be used for the same diagnostic and prognostic purposes as data relating to PRO213-1 gene expression. Therefore, based on the disclosure in the specification, no further research would be necessary to determine how to use the claimed PRO213-1 polypeptides, because the current invention is fully enabled by the disclosure of the present application.

Accordingly, Applicants submit that based on the general knowledge in the art at the time the invention was made and the teachings in the specification, the specification provides clear guidance as to how to interpret and use the data relating to PRO213-1 polypeptide expression and that the claimed PRO213-1 polypeptides have utility in the diagnosis of cancer.

A prima facie case of lack of utility has not been established

Applicants respectfully submit that the Examiner has not made a proper *prima facie* showing of lack of utility, because the Examiner has not shown that Applicants' asserted utility is more likely than not incorrect.

The Examiner asserts that "f[the] art discloses that a correlation between genomic DNA levels and mRNA levels cannot be presumed, nor can any correlation between genomic DNA levels and polypeptide levels", citing Pennica, Konopka, Sen, Godbout and Li (pages 5-8 of the instant Final Office Action).

² M.P.E.P. §2107 II(B)(1).

As a preliminary matter, Applicants respectfully submit that it is not a legal requirement to establish that gene amplification "necessarily" results in increased expression at the mRNA and polypeptide levels. As discussed in the previous responses of record, the evidentiary standard to be used throughout *ex parte* examination of a patent application is a preponderance of the totality of the evidence under consideration. Accordingly, Applicants submit that in order to overcome the presumption of truth that an assertion of utility by the applicant enjoys, the Examiner must establish that **it is more likely than not** that one of ordinary skill in the art would doubt the truth of the statement of utility. Therefore, it is not legally required that there be a "necessary" correlation between the data presented and the claimed subject matter. The law requires only that one skilled in the art should accept that such a correlation is **more likely than not to exist.** Applicants respectfully submit that when the proper evidentiary standard is applied, a correlation must be acknowledged.

Applicants have previously cited Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* as collectively teaching that in general, gene amplification increases mRNA expression. Further, Applicants' arguments directed to the references cited by the Examiner presented in the previously filed Responses are hereby incorporated by reference in their entirety.

Pennica *et al.*

The Examiner has cited the abstract of Pennica *et al.* for its disclosure that "WISP-2 DNA was amplified in colon tumors, but mRNA expression was significantly reduced in the majority of tumors compared with the expression in normal colonic mucosa from the same patient." (Page 5 of the instant Final Office Action). From this, the Examiner has concluded that increased copy number does not *necessarily* result in increased polypeptide expression. The standard, however, is not absolute certainty. The fact that in the case of a specific class of closely related molecules there seemed to be no correlation with gene amplification and the level of mRNA/protein expression, does not establish that it is more likely than not, in general, that such correlation does not exist.

Nowhere in the Pennica paper does the author suggest that it is more likely than not that altered mRNA levels does not correlate with altered protein levels. On the contrary, there is a statement in Pennica that says "[a]n analysis of WISP-1 gene amplification and expression in human colon tumors *showed a correlation between DNA amplification and over-expression...*"

(Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added), which implies that the mRNA/protein correlation does exist, even if not always, but “always” is not required by the utility standard.

The Examiner has not shown whether the lack or correlation observed for the family of WISP polypeptides is typical, or is merely a discrepancy, an exception to the rule of correlation. Indeed, the working hypothesis among those skilled in the art is that, if a gene is amplified in cancer, the encoded protein is likely to be expressed at an elevated level. In fact, as noted even in Pennica *et al.*, “[a]n analysis of *WISP-1* gene amplification and expression in human colon tumors showed a correlation between DNA amplification and over-expression . . .” (Pennica *et al.*, page 14722, left column, first full paragraph, emphasis added). Accordingly, Applicants respectfully submit that Pennica *et al.* teaches nothing conclusive regarding the absence of correlation between amplification of a gene and over-expression of the encoded WISP polypeptide. More importantly, the teaching of Pennica *et al.* is specific to *WISP* genes. Pennica *et al.* has no teaching whatsoever about the correlation of gene amplification and protein expression in general.

Konopka *et al.*

The Examiner has also cited the abstract of Konopka *et al.* to establish the assertion that protein expression is not related to gene amplification but to variation in the level of mRNA produced from a single genomic template. (Page 5 of the instant Final Office Action).

Regarding Konopka *et al.*, Applicants submit that the Examiner has completely misinterpreted the statement that “[p]rotein expression is not related to amplification of the *abl* gene but to variation in the level of *bcr-abl* mRNA produced from a single Ph¹ template.” (See Konopka *et al.*, Abstract). Konoka teaches that “[t]he demonstration that the Ph¹ chromosomal template can vary in its level of expression of P210 *c-abl* suggests that secondary mechanisms, beyond the translocation itself, contribute to the regulation of the *bcr-abl* gene in different cell types or subclones that derive from the affected stem cell.” (page 4049, 2nd column, 2nd paragraph) In an effort to characterize this differential expression, Konopka examined the production of the *abl* RNA via RNA blot hybridization analysis (Fig. 3), which “showed that the normal 6- and 7-kb *c-abl* mRNAs were present at a similar level in Ph¹-positive and -negative

cell lines derived from different patients." (page 4050, 2nd column, last paragraph) However, Konopka found that "the 8-kb mRNA that encodes P210 ^{c-abl} was detected at a 10-fold higher level in SK-CML7Bt-33 (Fig. 3A, +) than in SK-CML16Bt-1 (B, +), which correlated with the relative level of P210 ^{c-abl} detected in each cell line. Analysis of additional cell lines demonstrated that the level of 8-kb RNA directly correlated with the level of P210 ^{c-abl} (Table 1)" (page 4050, 2nd column, last paragraph; underlining added). As a further control, Konopka looked at DNA levels and found that "[t]he variation in level of 8-kb RNA detected in these cell lines was not due to loss or gain of Ph¹, because cytogenetic analysis confirmed the presence of Ph¹ in these cell lines." (page 4050, 2nd column, last paragraph) Konopka further established that "[t]here was no difference in the copy number of abl-related sequences as judged by Southern blot analysis (Fig. 4)." (page 4051, 1st column) From this study, Kopoka concludes "[t]hese combined data suggest that differential bcr-abl mRNA expression from a single gene template is responsible for the variable levels of P210 ^{c-abl} detected." (page 4051, 1st column) Therefore, the teachings of Konopka *et al.* are not pertinent to the examiner's argument because they are not directed towards the correlation of gene amplification and its gene product other than to demonstrate that there are mechanisms other than gene amplification that contribute to protein overexpression in cancer. However, Kopoka does support Applicants' position regarding a correlation between mRNA and protein levels.

Godbout *et al.*

*With respect to Godbout, the Examiner has asserted that Godbout *et al.* teaches that "a number of studies suggest that co-amplified genes are only overexpressed if they provide a selective advantage to the cells in which they are amplified." The Examiner further asserts that Godbout teaches "if it is generally accepted that co-amplified genes are not over-expressed unless they provide a selective growth advantage to the cell." (Pages 6-7 of the instant Final Office Action).*

Applicants have previously made of record three more recent references, published in 2002, by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* (made of record in Applicants' Response filed on October 4, 2004), which collectively teach that in general, gene amplification increases mRNA expression. Applicants submit that these more recent references must be acknowledged

as more accurately reflecting the state of the art regarding the correlation between gene amplification and transcript expression than the references cited by Godbout *et al.*

Applicants further maintain that Godbout *et al.* report that “there is a good correlation with DDX1 gene copy number, DDX1 transcript levels, and DDX1 protein levels in all cell lines studied.” Thus, in these cancer cell lines, DDX1 mRNA and protein levels are correlated.

Moreover, selective advantage to cell survival is not the only mechanism by which genes impact cancer. Mechanistic data is not a requirement for the utility requirement. Hence, this rejection is improper. Applicants respectfully submit that, as discussed above, Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (of record), collectively teach that gene amplification increases mRNA expression for large numbers of genes, which have not been identified as being oncogenes or as conferring any selective growth advantage on tumor cells. Thus, the art of record clearly shows that there is no requirement that a polypeptide must be a known oncogene or a protein otherwise known to be associated with tumor growth, in order for amplification of the gene encoding the protein to correlate with increased protein expression. In fact, as demonstrated by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, examination of gene amplification is a useful way to identify novel proteins not previously known to be associated with cancer.

Li et al.

The Examiner also cites Li et al. as teaching that “68.8% of the genes showing over-representation in the genome did not show elevated transcript levels.” (Page 7 of the instant Final Office Action).

Applicants respectfully point out that Li *et al.* acknowledge that their results differed from those obtained by Hyman *et al.* and Pollack *et al.* (of record), who found a substantially higher level of correlation between gene amplification and increased gene expression. The authors note that “[t]his discordance may reflect methodologic differences between studies or biological differences between breast cancer and lung adenocarcinoma” (page 2629, col. 1). In fact, as explained in the Supplemental Information accompanying the Li article, genes were considered to be amplified if they had a copy number ratio of at least 1.40. As discussed in Applicants’ previous responses, and in the Goddard Declaration of record, an appropriate

threshold for considering gene amplification to be significant is a copy number of at least 2.0. As discussed above, the PRO213-1 gene showed 2.04 fold to 46.9-fold amplification in adenocarcinomas or squamous cell carcinomas of the lung and colon, thus meeting this standard. It is not surprising that, by using a substantially lower threshold for considering a gene to be amplified, Li *et al.* would have identified a number of genes that were not in fact significantly amplified, and therefore did not show any corresponding increase in mRNA expression. The results of Li *et al.* therefore do not disprove that a gene with a substantially higher level of gene amplification, such as PRO213-1, would be expected to show a corresponding increase in transcript expression.

In response to Applicants' argument that the discordance may reflect methodologic differences, the Examiner asserts that "Li et al. did not limit their studies to genes that were amplified at less than 2-fold." In support of this assertion, the Examiner cites the first paragraph of the Supplemental Material. (Pages 15-16 of the instant Final Office Action).

Applicants respectfully point out that the Examiner has misinterpreted the methodology disclosed in the supplemental material. The evidence cited by the Examiner pertains to the inclusion criteria of the probes used for defining amplicons. In the second paragraph entitled "Relationship between genomic copy number and gene transcript level", the authors state that "[f]or each gene, the CGH data were represented by a vector that was labeled '1' for genomic overrepresentation (including amplification) ratio greater than 1.40 and '0' for no genomic overrepresentation." Nevertheless, the Examiner acknowledges that the alleged 2-fold amplification criteria would only apply to some of the samples. The Examiner has not established that a correlation does not exist in samples based solely on this threshold.

In summary, the Patent Office has failed to meet its initial burden of proof that Applicants' claims of utility are not substantial or credible. The arguments presented by the Examiner in combination with the cited articles do not provide sufficient reasons to doubt the statements by Applicants that PRO213-1 has utility. As discussed above, the law does not require that DNA amplification is "always" associated with overexpression of the gene product. Therefore, Applicants submit that the Examiner's reasoning is based on a misrepresentation of the scientific data presented in the above cited reference and application of an improper, heightened legal standard. In fact, contrary to what the Examiner contends, the art indicates that,

if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level.

It is "more likely than not" for amplified genes to have increased mRNA and protein levels

Applicants have submitted ample evidence to show that, in general, if a gene is amplified in cancer, it is more likely than not that the encoded protein will be expressed at an elevated level. First, the articles by Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.*, (of record) collectively teach that in general, gene amplification increases mRNA expression.

Second, Applicants have submitted over one hundred references, along with Declarations of Dr. Paul Polakis and Dr. Randy Scott (of record), which collectively teach that, in general, there is a correlation between mRNA levels and polypeptide levels.

Third, Applicants have submitted a recent decision by the Board of Patent Appeals and Interferences (Decision on Appeal No. 2006-1469), which acknowledged that “there is a strong correlation between mRNA levels and protein expression, and the Examiner has not presented any evidence specific to the PRO1866 polypeptide to refute that.” (Page 9 of the Decision). Applicants submit that, in the instant application, the Examiner has likewise not presented any evidence specific to the PRO213-1 polypeptide to refute Applicants’ assertion of a correlation between mRNA levels and protein expression.

Thus, taken together, all of the submitted evidence supports Applicants’ position that gene amplification is more likely than not predictive of increased mRNA and polypeptide levels.

The Examiner asserts that “Orntoft et al. could only compare the levels of about 40 well-resolved and focused abundant proteins.” (Page 11 of the instant Final Office Action; emphasis in original).

While technical considerations did prevent Orntoft *et al.* from evaluating a larger number of proteins, the ones they did look at showed a clear correlation between mRNA and protein expression levels. As Orntoft *et al.* states, “In general there was a highly significant correlation ($p<0.005$) between mRNA and protein alterations.... 26 well focused proteins whose genes had a known chromosomal location were detected in TCCs 733 and 335, and of these 19 correlated ($p<0.005$) with the mRNA changes detected using the arrays.” (See page 42, column 2 to page

34, column 2). Accordingly, Orntoft *et al.* clearly support Applicants' position that proteins expressed by genes that are amplified in tumors are useful as cancer markers.

The Examiner further asserts that "applicant has provided no fact or evidence concerning a correlation between the specification's disclosure of low levels of amplification of DNA (which were not characterized on the basis of those in the Orntoft publication) and an associated rise in level of the encoded protein." (Page 11 of the instant Final Office Action; emphasis in original).

As discussed in previous responses, the levels of amplification for PRO213-1 were **not** "low" but significant, and ranged from 2.0-fold to 3.05-fold, in three different lung tumors. Applicants note that the levels of gene amplification observed by Orntoft *et al.* were relatively low, averaging only 0.3-0.4-fold (page 40, col. 1). In particular, the level of gene amplification associated with expression changes was only around two-fold (see Figure 2), even less than the 2.0-fold to 3.05-fold amplification observed for PRO213-1. Even with these relatively low levels of gene amplification, Orntoft *et al.* found that "**[i]n most cases**, chromosomal gains detected by CGH were accompanied by an increased level of transcripts in both TCCs 733 (77%) and 827 (80%)" (page 40, col. 2; emphasis added). The level of correlation between DNA copy number and increased mRNA levels observed by Orntoft *et al.*, from 77-80%, clearly meets the standard of more likely than not. Orntoft *et al.* also found a "highly significant" correlation between mRNA and protein levels, with the two data sets studied having correlations of 39/40 (**98%**) and 19/26 (**73%**) (pages 42-43).

The Examiner asserts that "of the 12,000 transcripts analyzed, a set of 270 was identified in which overexpression was attributable to gene amplification." The Examiner concludes that "[t]his proportion is 2%; the Examiner maintains that 2% does not provide a reasonable expectation that the slight amplification of PRO213-1 would be correlated with elevated levels of mRNA." (Page 11 of the instant Final Office Action).

Applicants respectfully submit that the Examiner appears to have misinterpreted the results of Hyman *et al.* Hyman *et al.* chose to do a genome-wide analysis of a large number of genes, most of which, as shown in Figure 2, were not amplified. Accordingly, the 2% number is meaningless, as the low figure mainly results from the fact that only a small percentage of genes

are amplified in the first place. The significant figure is not the percentage of genes in the genome that show amplification, but the percentage of amplified genes that demonstrate increased mRNA and protein expression.

The Examiner further asserts that the Hyman reference "found 44% of highly amplified genes showing overexpression at the mRNA level, and 10.5% of highly overexpressed genes being amplified; thus, even at the level of high amplification and high overexpression, the two do not correlate." (Page 11 of the instant Final Office Action).

Applicants submit that the 10.5% figure is not relevant to the issue at hand. One of skill in the art would understand that there can be more than one cause of overexpression. The issue is not whether overexpression is always, or even typically caused by gene amplification, but rather, whether gene amplification typically leads to overexpression.

The Examiner's assertion is not consistent with the interpretation Hyman *et al.* themselves place on their data, stating that, "The results illustrate a **considerable influence of copy number on gene expression patterns.**" (page 6242. col. 1; emphasis added). In the more detailed discussion of their results, Hyman *et al.* teach that "[u]p to 44% of the highly amplified transcripts (CGH ratio, >2.5) were overexpressed (*i.e., belonged to the global upper 7% of expression ratios*) compared with only 6% for genes with normal copy number." (See page 6242, col. 1; emphasis added). These details make it clear that Hyman *et al.* set a highly restrictive standard for considering a gene to be overexpressed; yet almost half of all highly amplified transcripts met even this highly restrictive standard. Therefore, the analysis performed by Hyman *et al.* clearly shows that "it is more likely than not" that a gene which is amplified in tumor cells will have increased gene expression.

*The Examiner has also asserted that neither Hyman *et al.* nor Pollack *et al.* examines protein expression. (Page 11 of the instant Final Office Action).*

Applicants respectfully submit that the Orntoft *et al.*, Hyman *et al.* and Pollack *et al.* references were submitted primarily as evidence that in general, gene amplification increases mRNA expression. With regard to the correlation between mRNA expression and protein levels, Applicants previously submitted a Declaration by Dr. Polakis, principal investigator of the

Tumor Antigen Project of Genentech, Inc., the assignee of the present application, to show that mRNA expression correlates well with protein levels, in general.

With regard to the correlation between gene amplification, mRNA expression and protein levels, the Examiner has asserted that the Polakis Declaration is insufficient to overcome the rejection of claims 63, 69 and 70 since it is limited to a discussion of data regarding the correlation of mRNA levels and polypeptide levels and not gene amplification levels. The Examiner has further asserted that the declaration does not provide data such that the Examiner can independently draw conclusions. (Pages 12-13 of the instant Final Office Action).

Applicants submit that Dr. Polakis' Declaration was presented to support the position that there is a correlation between mRNA levels and polypeptide levels, the correlation between gene amplification and mRNA levels having already been established by the data shown in the Orntoft et al., Hyman et al., and Pollack et al. articles. Applicants emphasize that the opinions expressed in the Polakis Declaration, including the quoted statement, are all based on factual findings. Thus, Dr. Polakis explains that in the course of their research using microarray analysis, he and his co-workers identified approximately 200 gene transcripts that are present in human tumor cells at significantly higher levels than in corresponding normal human cells. Subsequently, antibodies binding to about 30 of these tumor antigens were prepared, and mRNA and protein levels were compared. In approximately 80% of the cases, the researchers found that increases in the level of a particular mRNA correlated with changes in the level of protein expressed from that mRNA when human tumor cells are compared with their corresponding normal cells. Dr. Polakis' statement that "an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell" is based on factual, experimental findings, clearly set forth in the Declaration. Accordingly, the Declaration is not merely conclusive, and the fact-based conclusions of Dr. Polakis would be considered reasonable and accurate by one skilled in the art.

The Examiner also asserts that the Polakis Declaration is allegedly contradicted by "strong opposing evidence," consisting of the various articles of record cited in previous Office Actions. (Pages 12-13 of the Final Office Action).

Applicants respectfully disagree and submit that, the utility standard is not absolute certainty. Appellants only need to show that it is **more likely than not** that an mRNA/protein

correlation exists in order to meet the utility standard. Therefore, even if a reasonable mRNA/protein correlation is not found in some instances, the utility standard can still be met in the instant application because Applicants have provided an overwhelming amount of evidences supporting a general mRNA/protein correlation. In contrast, the cited articles, and the reasons why they do not support the assertion of a lack of correlation between changes in mRNA levels and changes in protein levels, have been discussed in detail in Applicants' previous Responses. Accordingly, the evidence of the record has already established that it is "more likely than not" that increased mRNA levels predict increased protein levels.

The Examiner further notes (Page 13 of the instant Final Office Action) that Dr. Polakis is employed by the assignee.

Applicants respectfully submit that note the sworn Declaration of Dr. Polakis is sufficient to support Applicants' position a general mRNA/protein correlation, even if Dr. Polakis is an employee of the assignee.

The Examiner asserts that "[s]ince the Scott Declaration does not address the question of whether or not amplified genomic DNA is predictive of increased polypeptide levels, it is not considered pertinent to the rejection." (Page 13 of the instant Final Office Action).

Applicants respectfully submit that the Scott Declaration was submitted as evidence that in general, there is a correlation between mRNA levels and polypeptide levels. Evidence that in general, gene amplification increases mRNA expression is provided by other submissions of record, including, for example the Orntoft *et al.*, Hyman *et al.*, and Pollack *et al.* references (made of record) and Godbout *et al.* and Bea *et al.* (made of record).

Taken together, although there are some examples in the scientific art that do not fit within the central dogma of molecular biology that there is a correlation between polypeptide and mRNA levels, these instances are exceptions rather than the rule. In the majority of amplified genes, the teachings in the art, as exemplified by Orntoft *et al.*, Hyman *et al.*, Pollack *et al.*, and the Polakis and Scott Declarations, overwhelmingly show that gene amplification influences gene expression at the mRNA and protein levels. Therefore, one of skill in the art would reasonably expect in this instance, based on the amplification data for the PRO213-1 gene,

that the PRO213-1 polypeptide is concomitantly overexpressed. Thus, Applicants submit that the claimed PRO213-1 polypeptide have utility in the diagnosis of cancer.

Applicants therefore respectfully request withdrawal of the rejections of Claims 63, 69 and 70 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph.

CONCLUSION

In conclusion, the present application is believed to be in *prima facie* condition for allowance, and an early action to that effect is respectfully solicited. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

The Commissioner is hereby authorized to charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **07-1700**, referencing Attorney's Docket No. **123851-181893 (39780-2630 P1C4)**.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Respectfully submitted,

Date: August 22, 2008

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